REMARKS

The undersigned attorney has assumed responsibility for this application. Claims 93-98 and 133-156 are pending. Claims 133-156 have been added and claims 93 and 95-98 have been amended. Claims 1-92 and 99-132 have been canceled.

The amendments to claims 93 and 95-98 are supported by the specification and drawings as originally submitted. Specifically, consider pages 73 through 84. The new claims similarly find support at these pages. See also page 32, lines 1-9 and page 48, lines 8-18.

The claims pending in the parent application (claims 93-105) were rejected under 35 U.S.C. § 103 as being unpatentable over an article by Jonsson et al. (Nucleic Acids Research, 1993, Vol. 21, No. 3, 733-739). The claims as amended are distinguishable from the Jonsson et al. reference in multiple ways.

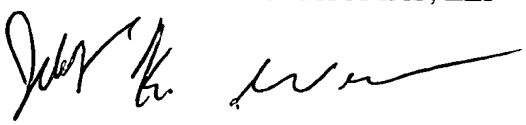
First, the claims employ sequences of two or more parental polypeptides or parental nucleic acids that encode polypeptides. The Jonsson et al. reference employs nucleic acid promoter sequences. The promoter sequences are neither polypeptides nor nucleic acids that encode polypeptides.

Second, the claims require "assessing structural stability of at least some of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids." Because the promoter sequences of the Jonsson et al. reference do not themselves encode polypeptides, the structural stability of encoded polypeptides cannot be assessed.

Each of the claims recites at least one other distinguishing feature. It respectfully submitted that the Jonsson et al. reference does not impact patentability of the presently pending claims. Withdrawal of the rejection is respectfully requested. Applicants are aware of no other prior art that suggests the claimed invention.

For the above reasons, it is respectfully submitted that pending claims 93-98 and 133-156 are allowable over the prior art. Applicants respectfully request a Notice of Allowance for this application. Should the Examiner believe that a telephone conference would expedite the prosecution of this application, the undersigned can be reached at the telephone number set out below.

Respectfully submitted,
BEYER WEAVER & THOMAS, LLP



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MARKED VERSON OF THE CLAIM AMENDMENTS

93. (Twice Amended) A method of producing recombinant [nucleic acids or] polypeptides or nucleic acids that encode polypeptides, the method comprising:

(a) providing data identifying sequences of two or more parental [nucleic acid or] polypeptides [sequences] or parental nucleic acids that encode polypeptides;

(b) computationally selecting one or more cross-over sites on the sequences of the two more parental polypeptides or parental nucleic acids for recombination [between the two or more parental nucleic acid or polypeptide sequences], thereby defining one or more [recombinant nucleic acids or] recombinant polypeptides or recombinant nucleic acids that result from a cross-over between at least two of the two or more parental [nucleic acids or] polypeptides or parental nucleic acids;

[determining a recombinant sequence for at least one of the one or more recombinant nucleic acids or polypeptides;]

(c) selecting [the] at least one of the recombinant [sequence] polypeptides or recombinant nucleic acids by computationally assessing three-dimensional structural stability of at least some of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids [*in silico* for one or more expected activity]; and

(d) synthesizing at least one portion of the [at least] one or more recombinant [sequence] polypeptides or recombinant nucleic acids selected in (c).

95. (Twice Amended) The method of claim 94, wherein synthesizing the at least one portion of the at least one selected recombinant [sequence] polypeptides or recombinant nucleic acids comprises providing fragments of the two or more parental nucleic acids and at least one of [corresponding] the bridge oligonucleotides, hybridizing the fragments and the bridge oligonucleotides and elongating the hybridized fragments with a polymerase or a ligase.

96. (Amended) The method of claim 93, wherein the two or more parental sequences display [low sequence similarity] less than about 50% identity.

97. (Twice Amended) The method of claim 93, wherein selecting the at least one recombinant [sequence in silico] polypeptide or recombinant nucleic acid in (c) comprises one or more of:

(i) performing an energy minimization analysis of the at least one recombinant [sequence] polypeptide;

(ii) performing a stability analysis of the [at least one recombinant sequence] recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids;

(iii) comparing an energy minimized model of the [at least one recombinant sequence] recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids to an energy minimized model of one or more of the two or more parental nucleic acids or polypeptides;

(iv) performing protein threading on one or more of the parental or recombinant polypeptides; and,

(v) selecting the cross-over sites for recombination between the two or more parental nucleic acid sequences or polypeptides to occur within regions of structural overlap, thereby determining the sequence of the at least one recombinant nucleic acid or polypeptide;

(vi) performing one or more of: PDA, a branch-and-terminate a combinatorial optimization analysis, a dead end elimination, a genetic or mean-field analysis, or analysis of protein folding by threading, of the [at least one recombinant sequence] recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids;

(vii) performing PDA of at least one of the two or more parental sequences; [or] and

(viii) comparing a PDA of the [at least one recombinant sequence] recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids to a PDA of at least one of the two or more parental sequences.

98. (Twice Amended) The method of claim 93, wherein (b) and (c) [the step of selecting cross-over sites for recombination between the two or more parental nucleic acid or polypeptide sequences and the step of selecting the at least one recombinant sequence in silico] are performed simultaneously.

APPENDIX OF ALL PENDING CLAIMS

1-92. Canceled.

93. (Twice Amended) A method of producing recombinant polypeptides or nucleic acids that encode polypeptides, the method comprising:

(a) providing data identifying sequences of two or more parental polypeptides or parental nucleic acids that encode polypeptides;

(b) computationally selecting one or more cross-over sites on the sequences of the two more parental polypeptides or parental nucleic acids for recombination, thereby defining one or more recombinant polypeptides or recombinant nucleic acids that result from a cross-over between at least two of the two or more parental polypeptides or parental nucleic acids;

(c) selecting at least one of the recombinant polypeptides or recombinant nucleic acids by computationally assessing three-dimensional structural stability of at least some of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids; and

(d) synthesizing at least one portion of the one or more recombinant polypeptides or recombinant nucleic acids selected in (c).

94. (Amended) The method of claim 93, further comprising providing bridging oligonucleotides which comprise or encode the cross-over sites.

95. (Twice Amended) The method of claim 94, wherein synthesizing the at least one portion of the at least one selected recombinant polypeptides or recombinant nucleic acids comprises providing fragments of the two or more parental nucleic acids and at least one of the bridge oligonucleotides, hybridizing the fragments and the bridge oligonucleotides and elongating the hybridized fragments with a polymerase or a ligase.

96. (Amended) The method of claim 93, wherein the two or more parental sequences display less than about 50% identity.

97. (Twice Amended) The method of claim 93, wherein selecting the at least one recombinant polypeptide or recombinant nucleic acid in (c) comprises one or more of:

(i) performing an energy minimization analysis of the at least one recombinant polypeptide;

(ii) performing a stability analysis of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids;

(iii) comparing an energy minimized model of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids to an energy minimized model of one or more of the two or more parental nucleic acids or polypeptides;

(iv) performing protein threading on one or more of the parental or recombinant polypeptides; and,

(v) selecting the cross-over sites for recombination between the two or more parental nucleic acid sequences or polypeptides to occur within regions of structural overlap, thereby determining the sequence of the at least one recombinant nucleic acid or polypeptide;

(vi) performing one or more of: PDA, a branch-and-terminate a combinatorial optimization analysis, a dead end elimination, a genetic or mean-field analysis, or analysis of protein folding by threading, of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids;

(vii) performing PDA of at least one of the two or more parental sequences; and

(viii) comparing a PDA of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids to a PDA of at least one of the two or more parental sequences.

98. (Twice Amended) The method of claim 93, wherein (b) and (c) are performed simultaneously.

99-132. Canceled.

133. (New) The method of claim 93, wherein computationally selecting one or more cross-over sites on the sequences of the two more parental polypeptides or nucleic acids for recombination comprises (i) identifying sites that correspond to overlapping amino acids in the parental polypeptides or (ii) identifying sites that will preserve selected subunits, domains, or motifs in the parental polypeptides.

134. (New) The method of claim 93, wherein (d) comprises synthesizing a set of oligonucleotides.

135. (New) The method of claim 134, wherein the set of oligonucleotides comprises one or more oligonucleotide member between about 20 and about 60 nucleotides in length.

136. (New) The method of claim 134, further comprising:

(e) recombining the set of oligonucleotides *in vitro* to generate a set of polynucleotide variants.

137. (New) The method of claim 136, wherein the polynucleotide variants are recombinant nucleic acids and wherein (e) comprises assembling a library of the recombinant nucleic acids parallel.

138. (New) The method of claim 136, wherein the polynucleotide variants are recombinant nucleic acids and wherein (e) comprises assembling a library of the recombinant nucleic acids by ligation of the oligonucleotides.

139. (New) A method of identifying a set of oligonucleotides for use in an *in vitro* recombination procedure, the method comprising:

(a) providing data identifying sequences of two or more parental polypeptides or parental nucleic acids that encode the polypeptides;

(b) computationally selecting one or more cross-over sites on the sequences based on structural information about the parental polypeptides or polypeptides encoded by the parental nucleic acids; thereby defining one or more recombinant polypeptides or recombinant nucleic acids that result from cross-overs between the parental polypeptides or nucleic acids at the one or more cross-over sites;

(c) selecting at least one of the recombinant polypeptides or recombinant nucleic acids by computationally assessing structural stability of at least some of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids; and

(d) computationally identifying one or more oligonucleotides for *in vitro* recombination by choosing at least one portion of at least one of the recombinant polypeptides or recombinant nucleic acids selected in (c).

140. (New) The method of claim 139, wherein the structural information employed in (b) comprises information depicting the three-dimensional structure of at least a portion of the parental polypeptides or polypeptides encoded by the parental nucleic acids.

141. (New) The method of claim 139, wherein (b) comprises selecting cross-over points that correspond to overlapping amino acids in the parental polypeptides.

142. (New) The method of claim 139, wherein (b) comprises selecting cross-over points at sites that will preserve selected subunits, domains, or motifs in the parental polypeptides.

143. (New) The method of claim 139, wherein (b) comprises selecting cross-over points at sites chosen to maintain or disrupt one ore more structural relationships between two or more amino acids in the parental polypeptides.

144. (New) The method of claim 139, further comprising performing an additional genetic operation on one or more of the parental or recombinant polypeptides or the parental or recombinant nucleic acids.

145. (New) The method of claim 144, wherein the genetic operation is selected from the group consisting of multiplication, mutation, fragmentation, and ligation.

146. (New) The method of claim 139, wherein at least one of the parental polypeptides or the parental nucleic acids comprise a naturally occurring polypeptide or a naturally occurring nucleic acid that encodes a polypeptide.

147. (New) The method of claim 139, wherein (c) comprises computationally assessing three-dimensional structural stability of at least some of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids.

148. (New) A computer program product comprising a machine readable medium on which is provided program instructions for identifying a set of oligonucleotides for use in an *in vitro* recombination procedure, the program instructions comprising:

(a) code for providing data identifying sequences of two or more parental polypeptides or parental nucleic acids that encode the polypeptides;

(b) code for selecting one or more cross-over sites on the sequences based on structural information about the parental polypeptides or polypeptides encoded by the parental nucleic acids; thereby defining one or more recombinant polypeptides or recombinant nucleic acids that result from cross-overs between the parental polypeptides or nucleic acids at the one or more cross-over sites;

(c) code for selecting at least one of the recombinant polypeptides or recombinant nucleic acids by assessing structural stability of at least some of the

recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids; and

(d) code for identifying one or more oligonucleotides for *in vitro* recombination by choosing at least one portion of at least one of the recombinant polypeptides or recombinant nucleic acids selected in (c).

149. (New) The computer program product of claim 148, wherein the structural information employed in (b) comprises information depicting the three-dimensional structure of at least a portion of the parental polypeptides or polypeptides encoded by the parental nucleic acids.

150. (New) The computer program product of claim 148, wherein (b) comprises code for selecting cross-over points that correspond to overlapping amino acids in the parental polypeptides.

151. (New) The computer program product of claim 148, wherein (b) comprises code for selecting cross-over points at sites that will preserve selected subunits, domains, or motifs in the parental polypeptides.

152. (New) The computer program product of claim 148, wherein (b) comprises code for selecting cross-over points at sites chosen to maintain or disrupt one ore more structural relationships between two or more amino acids in the parental polypeptides.

153. (New) The computer program of claim 148, further comprising code for performing an additional genetic operation on one or more of the parental or recombinant polypeptides or the parental or recombinant nucleic acids.

154. (New) The computer program product of claim 153, wherein the genetic operation is selected from the group consisting of multiplication, mutation, fragmentation, and ligation.

155. (New) The computer program product of claim 148, wherein at least one of the parental polypeptides or the parental nucleic acids comprise a naturally occurring polypeptide or a naturally occurring nucleic acid that encodes a polypeptide.

156. (New) The computer program product of claim 148, wherein (c) comprises code for assessing three-dimensional structural stability of at least some of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids.